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Disproportionation of aliphatic and aromatic aldehydes through Cannizzaro, Tishchenko, and Meerwein–Ponndorf–Verley reactions

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Abstract

Disproportionation of aldehydes through Cannizzaro, Tishchenko, and Meerwein–Ponndorf–Verley reactions often requires the application of high temperatures, equimolar or excess quantities of strong bases, and is mostly limited to the aldehydes with no CH_2 or CH_3 adjacent to the carbonyl group. Herein, we developed an efficient, mild, and multifunctional catalytic system consisting $AlCl_3/Et_3N$ in CH_2Cl_2 , that can selectively convert a wide range of not only aliphatic, but also aromatic aldehydes to the corresponding alcohols, acids, and dimerized esters at room temperature, and in high yields, without formation of the side products that are generally observed. We have also shown that higher $AlCl_3$ content favors the reaction towards Cannizzaro reaction, yet lower content favors Tishchenko reaction. Moreover, the presence of hydride donor alcohols in the reaction mixture completely directs the reaction towards the Meerwein–Ponndorf–Verley reaction.

Graphic abstract



Keywords Cannizzaro · Tishchenko · Meerwein-Ponndorf-Verley · Disproportionation · Aldehyde

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Introduction

The Cannizzaro reaction is one of the oldest processes in synthetic organic chemistry, involving the base-induced simultaneous oxidation–reduction of aldehydes into their corresponding alcohols and carboxylic acids. The original Cannizzaro reaction was carried out in the presence of equimolar or excess quantities of hydroxides or other strong bases and was limited to the aldehydes, which lack α -hydrogens [1]. This is due to the fact that the α -hydrogens of aliphatic aldehydes are acidic, and in the presence of strong base they can be removed to form an enolate, which can subsequently attack to the carbonyl group of another aldehyde to yield aldol products [2, 3]. Tishchenko reaction

has also a similar principle, yet the disproportionation products (alcohol and acid) undergo coupling process, which also has shown to be very challenging for aliphatic aldehydes due to harsh reaction conditions such as application of high temperatures, equimolar or excess of strong bases (i.e. aluminum alkoxides) [4-6]. Recently developed protocols involve the applications of Lewis acids [7], solid state [8], organoactinide [9, 10] and lanthanide [11] and imidazolin-2-iminato-Cp*thorium(IV) and aluminum [12] complexes, along with thiolate [13], selenide [14], polymeric ionic solvent [15], and metal catalysis [16], along with the aldol-Tishchenko reaction of sulfinimines [17] and lithium enolates [18]. Nevertheless, the disproportionation reaction of the aliphatic aldehyde, especially the ones with CH₂ or CH₃ adjacent to the carbonyl group are still elusive [3]. Disproportionation reaction of aldehydes, lacking α-hydrogens in the presence of Lewis acid (i.e. MgBr₂ and LiBr) and triethylamine (Et₃N) at room temperature has been previously reported [19, 20]. Despite offering mild conditions, those catalytic systems were still unable to disproportionate aliphatic aldehyde and preferentially give aldol products [2, 21]. Herein, we described a new catalytic system, which enables to selectively convert not only aliphatic, but also aromatic aldehydes to the corresponding alcohols, acids, and esters at room temperature (Scheme 1).

Results and discussion

Exposing aliphatic aldehyde, in particular, the ones with CH_2 or CH_3 adjacent to the carbonyl group to disproportionation reaction conditions preferentially leads to the formation of aldol products. This is due to the fact that the α -hydrogens of aliphatic aldehydes are acidic, and in the presence of strong base they can be removed to form an enolate, which can subsequently attack to the carbonyl group of another aldehyde to yield aldol products [2, 3]. Inspired by the original Tishchenko reaction of using Al(OR)₃ catalyst, and previously developed protocol of the Lewis acid/Et₃N system, we envisioned that the AlCl₃/Et₃N system could be utilized to perform such transformation.

Scheme 1



We initially explored the disproportionation reaction of benzaldehyde as a model aldehyde. Using catalytic amount of AlCl₃ (Table 1, entry 3) and 0.5 equivalent of Et₃N, we obtained 76% conversion of benzaldehyde to the respective alcohol/acid and ester. As the reaction mixture had a high viscosity, we reasoned that the addition of solvent could improve molecular collisions and consequently the conversion degree. Our results indicated that the conversion degree of the reaction is the highest for nonpolar solvent (CH₂Cl₂). Moreover, we tuned the concentration of the AlCl₃ in the reaction from 1:1 (Table 1, entry 7) to 1:100 (Table 1, entry 13) for RCHO: AlCl₃ ratio. We witnessed that the while the catalytic amount of Lewis acid leads to ester product (Tishchenko reaction), the higher amount favors the formation of corresponding alcohol and acid (Cannizzaro reaction) as shown in Table 1. We theorized that the AlCl₃ in a high concentration can coordinate two aldehydes, followed by nucleophilic attack of Et₃N to form a complex, and consequent conversion of those aldehydes to an alcohol and acid products upon aqueous workup. However, if used in a catalytic amount, AlCl₃ first can form the complex, and induce the hydride shift, then coordinate two other aldehydes and form new complex while dissociating from the first set (Scheme 2).

Such migration of AlCl₃ drives the nucleophilic attack of the alcohol to the unstable amide and leads to coupling

Table 1 Optimization of Cannizzaro/Tishchenko reaction

$$\mathbb{R} \xrightarrow{\mathsf{Et}_{3}\mathsf{N}} (\underbrace{\overset{\mathsf{0.5 equiv}}{\underset{\mathsf{AlCl}_{3} (\mathsf{n equiv})}{\mathsf{AlCl}_{3} (\mathsf{n equiv})}}_{\mathsf{Cannizzaro} (\mathsf{C})} \underbrace{\overset{\mathsf{0}}{\underset{\mathsf{C}}{\mathsf{P}}} \overset{\mathsf{0}}{\underset{\mathsf{C}}{\mathsf{P}}} \overset{\mathsf{0}}{{\mathsf{P}}} \overset{\mathsf{0}}{{\mathsf{P}}} \overset{\mathsf{0}}{{\mathsf{P}}} {\mathsf{C}}} {\mathsf{0}} {\mathsf{P}} {\mathsf{C}}} {\mathsf{C}} {\mathsf{P}} {\mathsf{C}} {\mathsf{C}} {\mathsf{P}}} {\mathsf{C}} {\mathsf{P}}} {\mathsf{C}} {\mathsf{C}}} {\mathsf{P}} {\mathsf{C}} {\mathsf{P}} {\mathsf{P}}} {$$

Entry	n	Solvent	Et ₃ N/eq	C ^a : T/%	Yield/% ^b
1	0.05	CH ₃ CN	0.5	4:45	48
2	0.05	CH ₃ CN	0.1	2:19	21
3	0.05	-	0.5	7:69	76
4	0.05	-	0.1	4:39	43
5	0.05	CH_2Cl_2	1	6:85	91
6	0.05	CH_2Cl_2	0.1	4:47	51
7	1	CH_2Cl_2	0.5	89:6	95
8	0.5	CH_2Cl_2	0.5	87:9	96
9	0.2	CH_2Cl_2	0.5	83:14	97
10	0.1	CH_2Cl_2	0.5	73:24	97
11	0.05	CH_2Cl_2	0.5	5:93	98
12	0.02	CH_2Cl_2	0.5	3:96	99
13	0.01	CH_2Cl_2	0.5	1:97	98

^aThe reaction yields were almost similar for alcohol and carboxylic acids products in the Cannizzaro reaction

^bMeasured by ¹H NMR analysis of the crude

Scheme 2



products. Moreover, while 0.5 equivalent of Et_3N is necessary for the reaction completion, the presence of an excess amount reduces the reaction rate and subsequently yield (Table 1, entry 5), possibly due to the fact that the excess Et_3N can complete more effectively for the Lewis acid and consequently lower the conversion yield.

Moreover, the disproportionation reaction has shown to present a higher yield in nonpolar CH_2Cl_2 solvent, compared to polar CH_3CN . This is highly likely due to complexation of N of CH_3CN by the Lewis acid, along with altering the free energy of the species in the polar media, requiring more activation energy for the reactants to reach the transition state apex. The reaction also can progress in the absent of solvent (Table 1, entries 3, 4), yet with comparatively lower yield. This may originate from higher viscosity of the reaction mixture in the absent of solvent, which can lower the chance of molecular collision and subsequently reduce the reaction yield. To better understand the reaction mechanism, we monitored the reaction progress as a function of time for the varying concentrations of AlCl₃ as shown in Fig. 1.

Initially, the conversion rate was greater for the reactions with higher concentrations of AlCl₃, favoring Cannizzaro reaction products (Fig. 1a, c). However, as the reaction progresses, the reaction with lower AlCl₃ concentration, supersede the ones with the higher content, and preferentially led to Tishchenko reaction products (Fig. 1b, c). This suggests that the formation of Al complex and the migration of AlCl₃ from one complex to a new set of aldehydes are fast. In addition, the higher viscosity of the mixture in the reactions with greater AlCl₃ content may decline the chance of molecular collision and reduce the reaction rate.

To realize the versatility of the reaction, we next subjected a variety of aldehydes to our disproportionation conditions. Both electron-rich (Table 2, entries 1, 2, 6, and

Fig. 1 Disproportionation of benzaldehyde through Cannizzaro **a** and Tishchenko reactions **b** in the presence Et_3N and varying amount of AlCl₃ catalyst as a function of time. **c** The overall conversion rate for disproportionation of benzaldehyde



Table 2	Switching Cannizzard	/Tishchenko reactior	s of aromatic and ali	phatic aldeh	ydes in the	presence of AlCl ₃ /	Et ₃ N
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	C JI R) _ `н	Et ₃ N (0.5 equi AlCl ₃ (n equiv) CH ₂ Cl ₂ , RT	v) () F C	OH ⁺ I	OH R & R 		R > (T)	
Entry	R	n	C ^a : T /%	Yield /% ^b	Entry	R	n	C ^a : T /%	Yield /% ^b
1	J)''	1	78:8	86	0	J'	1	52:5	57
		0.05	9:82	90	2		0.05	7:65	72
2	MeO	1	72:12	84	10	₹ S	1	57:6	63
		0.05	8:79	87	10		0.05	7:63	70
3	CI	1	80:10	90	11	~ ²²	1	81:7	88
		0.05	3:88	91			0.05	5:80	85
4	Br	1	91:1	92	12	<u>~</u> `ž	1	65:6	79
		0.05	87:7	94			0.05	7:67	81
5	O2N C	1	87:5	92	13	~~~ ² r ^č	1	86:6	92
		0.05	11:79	90			0.05	7:88	95
6	OMe	1	74:12	86	14	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	1	82:6	88
		0.05	9:81	90			0.05	7:84	91
7	() ^Y	1	77:7	84	15	, ^b ² i	1	73:6	72
		0.05	7:81	88			0.05	8:74	70
	N	1	75:8	83					
δ	L N	0.05	3:77	80					

^aThe reaction yields were similar for alcohol and carboxylic acids products in the Cannizzaro reaction

^bYields of isolated products characterized by ¹H NMR

7), electron-poor (entries 3-6) functionalized derivatives of benzaldehyde along with heterocyclic systems (entries 8–10), all underwent disproportionation reaction and gave excellent yields of conversion to corresponding esters or alcohol and acids, depending on the reaction conditions. Our data indicated that the substrates bearing electron-deficient aryl moieties gave a comparatively higher yield than those with electron-donating groups and heterocyclic aldehydes at room temperature. This is consistent with previous studies, suggesting that the hydride shift is still the rate determining step of the reaction [19]. However, we did not observe any correlation between the position of substituents (i.e. ortho vs. para) on the benzene ring and the reaction yield or direction towards Cannizzaro or Tishchenko products. Next, we probed whether aliphatic aldehydes would be amenable to disproportionation reaction. We were delighted to find the not only straight-chain systems (entries 11-14), but also the branched aliphatic aldehydes (entry 15) can also undergo Cannizzaro and Tishchenko reactions in good yields, without the formation of common aldol products. However, the conversion degree for both reactions was comparatively lower than those with the aryl moieties, due to their electron donating natures. To improve the reaction yield and time, we increased the AlCl₃ content to 0.2 equiv. However, while the aldehyde was completely consumed within 15 h, we witnessed the formation of isopropyl benzoate product, suggesting the disproportionation reaction (Cannizzaro or Tishchenko reactions) is competing with Meerwein–Ponndorf–Verley (MPV) reduction. On the other hand, elongating reaction time to 2 days improved the reaction yield to 92%.

To study the adaptability of the reaction condition, we also subjected a variety of aromatic and aliphatic aldehydes to adopted MPV reaction (Table 3). Our data showed that both electron-rich (Table 3, entries 1 and 2), electron-poor (entries 3–6) functionalized derivatives of benzaldehyde and heterocyclic systems (entries 6 and 7) along with aliphatic

Table 3 MPV reactions of aldehydes in the presence of $AlCl_3/Et_3N$

Entry R		Yield /% ^a	Entry R		Yield /%a	
1	Ń	78	9	N Y	88	
2	MeO	75	10	J.	68	
3	CI CI St	81	11	\sqrt{s}	74	
4	Br	82	12	~ ²⁵	79	
5		92	13	Śź	82	
6	OMe	73	14	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	81	
7		79	15	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	£ 83	
8		91	16	, is a second	72	

^aYields of isolated alcohols characterized by ¹H NMR

aldehydes (entries 8–12) all underwent MPV reaction with high yields of conversion. This indicates that the $AlCl_3/Et_3N$ is a mild and versatile catalytic system for disproportionation of both aliphatic and aromatic aldehydes into alcohol, acid, and ester products.

Conclusion

We have shown that AlCl₃/Et₃N is an efficient and mild catalytic system to selectively convert the aliphatic and aromatic aldehydes to the corresponding alcohols, acids, and esters through Cannizzaro, Tishchenko, and MPV reactions at room temperature. This system not only has the advantage of using very inexpensive reactants, in very mild conditions, which are crucial for large-scale synthesis, but also affords the desired products with very high yields without formation of the side products that are generally detected under other conditions. The application of the AlCl₃/Et₃N for asymmetric disproportionation of the aldehydes into esters and alcohol/acids are currently being investigated to extend the versatility of the present system and expected to offer a better mechanistic understanding of this transformation.

Experimental

All chemicals were purchased from Sigma-Aldrich. The aldehydes were distilled with bubble distillation and kept under inert atmosphere (argon) prior to the reactions. The CH_2Cl_2 was treated with CaH_2 overnight and distilled prior to addition to the reaction. Anhydrous $AlCl_3$ (> 99%) and trimethylamine (> 99.5%) were used as purchased without any further purification yet under argon atmosphere. ¹H NMR spectra were recorded on Bruker DMX 500 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard. GC–MS analysis was performed on Agilent 6890 (GC)/5972A (MS). Melting point measurements were performed on FisherbrandTM Digital Melting Point apparatus, and boing points was assessed with standard distillation method.

General experimental methods for AlCl₃-catalyzed Cannizzaro/Tishchenko reactions

A mixture of AlCl₃ (0.5 mmol), the aldehyde (10 mmol), and triethylamine (5 mmol) was added to 2 cm³ of dried CH₂Cl₂ and stirred for 2 days at room temperature under argon atmosphere until the aldehyde was completely consumed. The reaction progress was probed by TLC and GC/MS (Agilent 6890 (GC)/5972A (MS)). The reaction mixture was then filtered through Whatman filter paper (grade 2), and treated with sodium bicarbonate solution, followed by isolating the organic phase via a separatory funnel. The aqueous phase washed several times with CH₂Cl₂ to make sure that all organic materials extracted. Then, the organic phase was dried using sodium sulfate and subsequently analyzed by GC/MS and ¹H NMR, and validated using melting or boiling point of the product.

General experimental methods for AlCl₃ catalyzed Meerwein–Ponndorf–Verley (MPV) reactions

A mixture of AlCl₃ (0.1–10 mmol), the aldehyde (10 mmol), triethylamine (10 mmol) and isopropanol (10 mmol) was added to 2 cm³ of dried CH_2Cl_2 and stirred for 2 days at room temperature under argon atmosphere until the aldehyde was completely consumed. The reaction progress was monitored by TLC and GC/MS. The reaction mixture was then filtered, and treated with sodium bicarbonate solution, followed by isolating the organic phase via a separatory funnel. The aqueous phase washed several times with CH_2Cl_2 to ensure that all organic materials extracted. Then, the organic phase was dried over sodium sulfate, and subsequently analyzed by GC/MS and ¹H NMR and validated using melting or boiling point of the product.

Isolation of the components

To isolate the products of the reactions, first the reaction mixture was filtered and then treated with NaH₂PO₄ solution. Nest, the organic phase was separated via a separatory funnel, and the aqueous phase washed several times with CH₂Cl₂ to ensure that all organic materials were extracted. Afterward, the organic phase was dried over sodium sulfate. The reaction components of aromatic reactants (Table 2: entry 1-10 and Table 3: entry 1-11) were separated via flash column chromatography over silica gel 60 (0.040–0.063 mm; 230–400 mesh ASTM). The starting mobile phase was hexane:ethylacetate (4:1) to elute and separate aldehydes, alcohols, and esters, followed by the second mobile phase solution (ethyl acetate:methanol (10:1)) to elute the carboxylic acids. The reaction components of aliphatic reactants (Table 2: entry 11-15 and Table 3: entry 12–16) were separated via bulb to bulb distillation.

Reaction rate study

To study the Cannizzaro/Tishchenko reaction rate, we made a series of reaction mixtures of benzaldehyde (100 mmol), and triethylamine (50 mmol) in 20 cm³ of dried CH₂Cl₂ along with varying amount of AlCl₃ (i.e. 2, 5, 10, 20, 50, and 100 mmol). The reaction mixtures were stirred at room temperature under argon atmosphere, and 2 cm³ of each reaction mixture was removed at each time points (i.e. 1, 2, 4, 8, 16, 24, and 48 h) from the flask, followed by filtration and washing with sodium bicarbonate. The resultant samples were dried over sodium sulfate and analyzed using GC/MS. The reaction rate study was triplicated and the conversion degree for each reaction mixture was calculated from the average concentration the products in the reaction mixtures, using GC/MS spectra.

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